UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 07-SEP-2016

SUBJECT: **Glyphosate.** Completion and submission of toxicology data evaluation records.

PC Code: 417300; 103601; 103603; 103604; 103605; 103607; 103608; 103613
Decision No.: 521023
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0057492

MRID No.: See Table

DP Barcode: D435568

Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 41071-83-6; 38641-94-0; 70393-85-0; 114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7; 70901-12-1
40 CFR: §180.364

FROM: Anwar Y. Dunbar, Ph.D.
Pharmacologist, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)

THROUGH: Kelly Lowe, Acting Branch Chief
Risk Assessment Branch 1 (RAB1)
Health Effects Division (HED; 7509P)

TO: Khue Nguyen, Risk Manager Reviewer
Neil Anderson, Risk Manager
Pesticide Registration Division (RD; 7508P)

I. CONCLUSIONS

RAB1 has reviewed the submitted cancer and metabolism studies for the active ingredient Glyphosate. The study types and classifications are listed in the table below.

II. ACTION REQUESTED

Please review the submitted cancer and metabolism for Glyphosate.

Table 1. Submitted Toxicology Studies for Glyphosate

Guideline Toxicology Studies

Study Type	MRID	Classification
Carcinogenicity Study in Mice 870.4200b	49957402 (2009)	Acceptable/Guideline
Carcinogenicity Study in Mice 870.4200b	49987403 (1997)	Unacceptable/Guideline
Chronic/Carcinogenicity Study in Rats 870.4300	49957404 (1994)	Acceptable/Guideline
Chronic/Carcinogenicity Study in Rats 870.4300	49987401 (1994)	Acceptable/Guideline
ADME following Single Dose 870.7485	44320620 (1996)	Acceptable/Guideline
ADME following Single Dose 870.7485	44320621 (1996)	Acceptable/Guideline
ADME following Single Dose 870.7485	44320622 (1996)	Acceptable/Guideline
ADME following Single Dose 870.7485	44320623 (1996)	Acceptable/Guideline
ADME following Repeated Dose 870.7485	44320624 (1996)	Acceptable/Guideline
ADME following Single Dose 870.7485	44320625 (1996)	Acceptable/Guideline
ADME following Single Dose 870.7485	47007908 (1996)	Acceptable/Guideline

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:**
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Carcinogenicity Study in Mice – Mouse (83-2)

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 49957402

TEST MATERIAL (Purity): Glyphosate (95.7%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Wood, E., Dunster, J., Watson, P., and Brooks, P. (2009) Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. Unpublished.

SPONSOR: Nufarm Asia Sdn Bhd, L2.03 Wisma BU8, No. 11, Lebuh Bandar Utama, 47800 Paetaling Jayah, Selangor DE, Malaysia

EXECUTIVE SUMMARY:

In a feeding study conducted in 2009 (MRID 49957402), CD-1 mice (50/sex/dose) received glyphosate (94.6–97.6%) at 0, 500, 1500, or 5000 ppm for 18 months (0, 85, 267 or 946 mg/kg/day [M/F]). No groups were established for interim sacrifice and tissue analysis. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

There were no treatment-related effects on mortality. There were no treatment-related effects on clinical signs of toxicity, absolute bodyweights, food consumption, proportion of palpable masses, hematology, organ weights, necropsy, and histopathology. There were no treatment-related pre-neoplastic or related non-neoplastic lesions in this study.

The agency searched the pathology report to identify tumors types with potential monotonic dose responses. Lung adenomas and adenocarcinomas, and malignant lymphomas were identified for further analyses. Statistical analyses of lung adenomas, adenocarcinomas, and combined adenomas/adenocarcinomas are presented in Table 1. A statistically significant trend was noted for the adenocarcinomas. Closer examination of the tumor incidence indicates the dose-response was relatively flat at the low- and mid-dose with only an increase observed at the high-dose;

however, the incidence of lung adenocarcinomas at the high-dose (810 mg/kg/day) was not statistically significant when compared to the concurrent controls.

Table 1. Lung Tumors in Male CD-1 Mice
Fisher's Exact Test and Cochran-Armitage Trend Test Results.

Dose (mg/kg/day)	0	71.4	234.2	810
Lung Adenoma Incidence	9/51	7/51	9/51	4/51
(%)	(18)	(14)	(18)	(8)
Raw p-value =	-[b]	0.793	0.602	0.964
Sidak p-value =	-	0.991	0.937	1.000
Lung Adenocarcinoma	5/51[a]	5/51	7/51	11/51
(%)	(10)	(10)	(14)	(22)
Raw p-value =	0.028*	0.630	0.380	0.086
Sidak p-value =	--	0.949	0.762	0.237
Lung Combined Incidence	14/51	12/51	16/51	15/51
(%)	(27)	(24)	(31)	(29)
Raw p-value =	0.336	0.752	0.414	0.500
Sidak p-value =	--	0.985	0.799	0.875

Note: Trend test results denoted at control; * denotes significance at p=0.05;** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined.
b = Trend p-value not reported since tumor incidence decreased with increasing dose.

Tumor incidence for malignant lymphoma are presented in Table 2. A statistically significant trend was observed and the incidence at the high-dose (810 mg/kg/day) was statistically significantly elevated as compared to concurrent controls with the raw (unadjusted) p-value; however, with an adjustment for multiple comparisons, the increased incidence at the high-dose was not statistically significant (p= 0.082).

Table 2. Malignant Lymphomas in Male CD-1 Mice
Fisher's Exact Test and Cochran-Armitage Trend Test Results.

Dose (mg/kg/day)	0	71.4	234.2	810
Malignant Lymphoma Incidence	0/51	1/51	2/51	5/51
(%)	(0)	(2)	(4)	(10)
Raw p-value =	0.007**	0.500	0.248	0.028*
Sidak p-value =	--	0.875	0.574	0.082

Note: Trend test results denoted at control; * denotes significance at p=0.05;** denotes significance at p=0.01
a= Number of tumor bearing animals/Number of animals examined.

In appendix 1, the total tumor incidences are listed for males and females respectively.

The NOAEL is ≥ 5000 ppm. A LOAEL was not established.

The neoplastic lesions in this study are not considered treatment-related.

CLASSIFICATION

This carcinogenicity study in CD-1 mice is **Acceptable/Guideline** and satisfies the guideline

requirement for a carcinogenicity study [OCSPP 870.4200; OECD 451] in mice.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. A Data Confidentiality statement was not located in the study report.

Appendix 1 – Incidence and % Incidence of Neoplastic Lesions by Tissue for Terminal Kill and Interim Death Animals Combined (Page 57 of the Study Report)

Sex & Dose Groups	MALES										FEMALES									
	0ppm		500ppm		1500ppm		5000ppm				0ppm		500ppm		1500ppm		5000ppm			
Number of Mice	51		51		51		51				51		51		51		51			
CONDITION	n	%	n	%	n	%	n	%			n	%	n	%	n	%	n	%		
MESENTERIC LYMPH NODE																				
Histiocytic sarcoma m	0	0	0	0	0	0	0	0			2	4	0	0	0	0	1	2		
OVARY																				
Luteoma b											1	2	1	2	1	2	1	2		
Haemangioma b											0	0	0	0	0	0	1	2		
Sertoli cell tumour b											0	0	0	0	0	0	1	2		
Cystadenoma b											0	0	0	0	0	0	2	4		
Anaplastic sarcoma m											0	0	1	2	0	0	0	0		
PANCREAS																				
Islet cell adenocarcinoma m	0	0	0	0	0	0	0	0			1	2	0	0	0	0	0	0		
PITUITARY																				
Adenoma b	0	0	0	0	0	0	0	0			0	0	1	2	0	0	2	4		
SEMINAL VESICLE																				
Adenoma b	2	4	0	0	0	0	0	0												
Leiomyosarcoma m	0	0	0	0	0	0	1	2												
SKIN/SUBCUTIS																				
Fibrosarcoma m	0	0	3	6	2	4	1	2			0	0	0	0	0	0	0	0		
Haemangiosarcoma m	0	0	0	0	0	0	0	0			0	0	1	2	0	0	0	0		
SPLEEN																				
Haemangioma b	1	2	0	0	0	0	0	0			0	0	0	0	0	0	0	0		
Haemangiosarcoma m	0	0	0	0	0	0	0	0			1	2	0	0	0	0	1	2		
TESTIS																				
Interstitial cell tumour b	2	4	0	0	0	0	0	0												
THYMUS																				
Histiocytic sarcoma m	0	0	0	0	0	0	0	0			0	0	0	0	1	2	0	0		
UTERUS																				
Endometrial stromal polyp b											2	4	2	4	3	6	4	8		
Haemangioma b											0	0	1	2	0	0	0	0		
Leiomyoma b											0	0	0	0	1	2	0	0		
Squamous cell carcinoma m											1	2	0	0	0	0	0	0		
Histiocytic sarcoma m											2	4	2	4	0	0	1	2		
Leiomyosarcoma m											1	2	0	0	0	0	0	0		

Appendix 1 (Continued) – Incidence and % Incidence of Neoplastic Lesions by Tissue for Terminal Kill and Interim Death Animals Combined (Page 58 of the Study Report)

Sex & Dose Groups	MALES										FEMALES									
	0ppm		500ppm		1500ppm		5000ppm		0ppm		500ppm		1500ppm		5000ppm	
Number of Mice	51		51		51		51		51		51		51		51	
CONDITION	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ABDOMINAL																
Lipoma b	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0
Mesothelioma m	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Anaplastic sarcoma m	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
LYMPHOID/HAEMOPOIETIC ***																
Myeloid leukaemia m	0	0	1	2	0	0	0	0	0	0	0	0	1	2	0	0
Malignant lymphoma m	0	0	1	2	2	4	5	10	11	22	8	16	10	20	11	22
****Histiocytic sarcoma m	0	0	0	0	0	0	0	0	4	8	2	4	1	2	3	6
Combined	0	0	2	4	2	4	5	10	15	29	10	20	12	24	14	28
OVERALL TUMOUR INCIDENCE																
Primary benign tumours	15	29	6	12	9	18	7	14	5	10	6	12	6	12	9	18
Primary malignant tumours	14	28	20	39	17	33	20	39	23	45	15	29	16	31	18	35
Multiple benign tumours	6	12	2	4	4	8	1	2	4	8	4	8	1	2	7	14
Multiple malignant tumours	1	2	2	4	3	6	5	10	4	8	2	4	1	2	1	2

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:** Ray Kent
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Carcinogenicity Study in Mice (IET 94-0151) – Mouse (83-2)

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 49987403

TEST MATERIAL (Purity): Glyphosate (95%)

SYNONYMS:

CITATION: Kumar, D.P.S. (1997), Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice, Toxicology Department Rallis Research Centre, Rallis India Limited. Study No. TOXI: 1559.CARCI-M. No MRID 49987403. Unpublished.

SPONSOR: M/s Fiechemie Schwebda GmbH, Eupener Strabe 150, 50933, KOLN, Germany

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID 49987403), male and female Swiss Albino mice (50/sex/dose) were administered glyphosate (Technical) in the diet at 0, 100, 1000, and 10000 ppm (0, 14.5/15.0, 150/151, 1454/1467 mg/kg/day [M/F]). Throughout the experimental period, the mice were observed for: appearance, behavior, clinical/toxic signs, eye afflictions, neurological changes, physical abnormalities, growth, food consumption, survival and mass formation. Tissue weights, gross necropsy and histopathological analysis were determined throughout the study and at study termination. Blood smears were prepared from all surviving animals at 9 and 18 months of the study period for differential leukocyte count analysis. Blood smears were also prepared from animals which were found in moribund condition before they were exsanguinated. Tissues of all mice from: the control and high dose groups, all the dead and moribund sacrificed mice, and all gross lesions and masses from all mice were examined for histopathological changes.

Excess mortality was observed at the high-dose. For males there were 27 pre terminal deaths in the high-dose group vs. 22 in the control (54% vs. 44%). For females there were 20 pre terminal deaths

in the mid- and high-dose groups vs. 16 in the control (both 40% vs. 32%). There were no treatment-related effects on clinical signs, behavior, eyes, body weight, absolute body weights and body weight gains, food consumption, and differential white blood cell counts in both sexes. Gross pathology, organ weight data, and histopathological examination demonstrated no treatment-related effects.

There were more than 50 datasets in which there was at least 1 tumor, though none showed a monotonic dose response. Malignant lymphomas, one of the most common spontaneous neoplastic lesions in aging mice (Brayton et al., 2012), were reported in all dose groups, with only a slight increase in incidence in high-dose males. Murine leukemia viruses (MuLVs) are known to be a common cause of lymphoma in many different strains of mice (Ward, 2006) and may have potentially impacted this study. Tadesse-Heath et al. (2000) for example reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice infected with MuLVs.

Based upon the effects in this study, the LOAEL is 1454 mg/kg bw/day based upon increased mortality. The NOAEL is 151 mg/kg bw/day.

***A potential viral contamination of the colonies was noted and it's not clear how this impacted the study results.**

CLASSIFICATION

This carcinogenicity study in mice is **Unacceptable/Guideline** and based upon increased mortality at the highest dose tested in both sexes and does not satisfy the guideline requirement for a carcinogenicity study [OCSPP 870.4200; OECD 451] in mice.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. A Data Confidentiality statement was not located in the study report.

References:

Brayton CF, Treuting PM, Ward JM (2012). Pathobiology of aging mice and GEM: background strains and experimental design. Vet Pathol, 49, 85-105.

Taddesse-Heath L., Chattopadhyay SK, Dillehay DL, Lander MR, Nagashfar Z, Morse HC, III, Hartley JW (2000). Lymphomas and high-level expression of murine leukemia viruses in CFW mice. J Virol, 74, 6832-7.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:** Ray Kent
Senior Scientist, Health Effects Division (7509P) **Date:** 9/1/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: 24-Month Oral Chronic Toxicity and Carcinogenicity Study in Rats – Rat (83-5)

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 49957404

TEST MATERIAL (Purity): Glyphosate (95.7%)

SYNONYMS:

CITATION: Wood, E., Dunster, J., Watson, P., and Brooks, P. (2009) Glyphosate Technical: Dietary Combined Chronic Toxicity/Carcinogenicity Study in the Rat. Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-012. April, 23, 2009. MRID 49957404. Unpublished.

SPONSOR: Nufarm Asia Sdn Bhd, L2.03 Wisma BU8, No. 11, Lebuh Bandar Utama, 47800 Paetaling Jayah, Selangor DE, Malaysia

E XECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study (MRID 49957404), glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group, and three corresponding satellite groups (15 rats/sex/group) received diets containing 0, 1500, 5000, and 15,000 ppm glyphosate for 24 months (52 weeks for the satellite groups). To ensure that a limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24000 ppm. The achieved doses were: 0, 86/105, 285/349 or 1077/1382 mg/kg/day (M/F). Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination. No adverse effects on survival were seen in either sex across the doses tested.

The agency searched of the pathology report to identify tumors types with potential monotonic dose responses, and in female rats, mammary gland tumors were identified for further analysis. Tumor incidences for mammary gland adenomas, adenocarcinomas, and combined

adenomas/adenocarcinomas in female rats are presented in Table 1. Statistically significant trends were observed for the adenocarcinoma and combined analyses. The tumor incidence for adenocarcinomas was not statistically significant in pairwise comparisons as compared to concurrent controls. Marginal statistical significance was observed with the raw (unadjusted) p-value for combined mammary gland tumors at the high-dose (1229.7 mg/kg/day) when comparing to concurrent controls; however, with an adjustment for multiple comparisons, the increased incidence at the high-dose was not statistically significant (p=0.132).

Table 1. Mammary Gland Tumor Incidences in Female Rats
Fisher's Exact Test and Cochran-Armitage Trend Test Results

Tumor Type	0 mg/kg/day	95.0 mg/kg/day	316.9 mg/kg/day	1229.7 mg/kg/day
Adenoma				
Incidence	0/51	0/51	0/51	2/51
(%)	(0)	(0)	(0)	(4)
Raw p-value =	0.062	1.000	1.000	0.248
Sidak p-value =	--	1.000	1.000	0.248
Adenocarcinoma				
Incidence	2/51	3/51	1/51	6/51
(%)	(4)	(6)	(2)	(12)
Raw p-value =	0.042*	0.500	0.879	0.135
Sidak p-value =	--	0.875	0.998	0.352
Combined				
Incidence	2/51	3/51	1/51	8/51
(%)	(4)	(6)	(2)	(16)
Raw p-value =	0.007**	0.500	0.879	0.046*
Sidak p-value =	--	0.875	0.998	0.132

Note: Trend test results denoted at control; * denotes significance at p=0.05; ** denotes significant at p=0.01.

In appendix 1, the total tumor incidences are listed for males and females, respectively.

Based on the effects in this study, the NOAEL is ≥ 1077/1382 mg/kg/day. A LOAEL was not established. Transient liver enzyme activity for mid-dose males and high-dose males and females were observed, in addition to increased adipose infiltration of the bone marrow in high-dose males. Both effects were not considered adverse.

There was no evidence of treatment-related neoplastic lesions in this study.

CLASSIFICATION

This chronic/carcinogenicity study in rats is **Acceptable / Guideline** and satisfies the guideline requirement for a carcinogenicity study [OCSPP 870.4200; OECD 451] in rats.

Appendix 1 – Incidence and % Incidence of Neoplastic Lesions by Tissue for Terminal Kill and Interim Death Animals Combined (Page 60 of the Study Report)

	MALES								FEMALES							
	0ppm		1500ppm		5000ppm		15000ppm		0ppm		1500ppm		5000ppm		15000ppm	
Number of Rats	51		51		51		51		51		51		51		51	
CONDITION	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ADRENAL GLAND																
Cortical adenoma b	1	2	1	2	0	0	0	0	1	2	1	2	0	0	0	0
Cortical carcinoma m	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Phaeochromocytoma b	0	0	0	0	0	0	2	4	0	0	0	0	0	0	0	0
Phaeochromocytoma m	2	4	0	0	3	6	0	0	0	0	0	0	0	0	0	0
Ganglioneuroma b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
BONE																
Osteoma b	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
BRAIN/SPINAL CORD																
Astrocytoma m	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Granular cell tumour b	1	2	1	2	0	0	0	0	0	0	0	0	0	0	0	0
Granular cell tumour m	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Oligodendroglioma b	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0
Ependymoma m	0	0	0	0	0	0	0	0	1	2	1	2	0	0	0	0
INTESTINAL TRACT																
Leiomyoma b	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0
Leiomyosarcoma m	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
EPIDIDYMIS																
Mesothelioma b	1	2	0	0	0	0	0	0								
Mesothelioma m	0	0	2	4	0	0	0	0								
HEART																
Schwannoma m	0	0	1	2	0	0	0	0	2	4	0	0	0	0	0	0
KIDNEY																
Lipoma b	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Tubular carcinoma m	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Clear cell carcinoma m	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0
LIVER																
Hepatocellular adenoma b	0	0	2	4	1	2	1	2	1	2	0	0	1	2	1	2
Hepatocellular carcinoma m	1	2	0	0	0	0	0	0	0	0	0	0	1	2	0	0
Cholangioma b	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0
LYMPH NODE																
Angioma b	7	14	4	8	1	2	6	12	3	6	1	2	0	0	1	2
Angiosarcoma m	4	8	0	0	2	4	0	0	0	0	0	0	0	0	0	0

Appendix 1 (Continued) – Incidence and % Incidence of Neoplastic Lesions by Tissue for Terminal Kill and Interim Death Animals Combined (Page 63 of the Study Report)

	MALES										FEMALES									
	0ppm		1500ppm		5000ppm		15000ppm		0ppm		1500ppm		5000ppm		15000ppm					
Number of Rats	51		51		51		51		51		51		51		51					
CONDITION	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%				
MAMMARY GLAND																				
Fibroadenoma b									7	14	9	18	7	14	5	10				
Adenoma b									0	0	0	0	0	0	2	4				
Adenocarcinoma m									2	4	3	6	1	2	6	12				
Total									9	18	12	24	8	16	13	26				
NASAL CAVITIES																				
Polypoid adenoma b	2	4	1	2	0	0	0	0	0	0	0	0	0	0	0	0				
OVARY																				
Granulosa cell tumour b									3	6	0	0	1	2	0	0				
Granulosa-theca cell tumour b									1	2	3	6	0	0	0	0				
Anaplastic sarcoma m									1	2	0	0	0	0	0	0				
PANCREAS																				
Islet cell adenoma b	4	8	1	2	2	4	1	2	0	0	0	0	0	0	0	0				
Islet cell adenocarcinoma m	0	0	0	0	0	0	0	0	0	0	0	0	1	2	0	0				
PARATHYROID																				
Adenoma b	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
PAROTID SALIVARY GLAND																				
Acinar adenoma b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
PHARYNX																				
Squamous papilloma b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2				
PITUITARY																				
Adenoma b	16	31	11	22	10	20	20	39	24	47	23	45	16	31	32	63				
Adenocarcinoma m	1	2	0	0	0	0	0	0	0	0	1	2	0	0	0	0				
SKIN - SUBCUTANEOUS																				
Fibroma b	0	0	1	2	2	4	0	0	0	0	0	0	1	2	0	0				
Fibrosarcoma m	2	4	2	4	3	6	0	0	0	0	0	0	0	0	0	0				
Histiocytic sarcoma m	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0				
Lipoma b	0	0	0	0	1	2	0	0	0	0	1	2	0	0	1	2				
Leiomyosarcoma m	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0				
Angioma b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4				

Appendix 1 (Continued) – Incidence and % Incidence of Neoplastic Lesions by Tissue for Terminal Kill and Interim Death Animals Combined (Page 64 of the Study Report)

	MALES								FEMALES							
	0ppm		1500ppm		5000ppm		15000ppm		0ppm		1500ppm		5000ppm		15000ppm	
Number of Rats	51		51		51		51		51		51		51		51	
CONDITION	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
SKIN - CUTANEOUS																
Basal cell tumour b	1	2	0	0	0	0	0	0	1	2	0	0	0	0	0	0
Squamous cell carcinoma m	3	6	0	0	0	0	1	2	0	0	0	0	1	2	0	0
Keratoacanthoma b	2	4	3	6	0	0	6	12	0	0	0	0	0	0	0	0
Sebaceous adenoma b	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0
Sebaceous adenocarcinoma m	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0
Trichoepithelioma b	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0
Squamous papilloma b	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
*Sebaceous-squamous carcinoma m	0	0	1	2	0	0	0	0	0	0	1	2	0	0	0	0
SPLEEN																
Angioma b	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
Angiosarcoma m	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
STOMACH																
Squamous papilloma b	1	2	0	0	2	4	1	2	0	0	1	2	0	0	0	0
TESTIS																
Interstitial cell tumour b	2	4	3	6	1	2	1	2								
THYMUS																
Lymphocytic thymoma b	0	0	0	0	1	2	1	2	7	14	2	4	4	8	3	6
Lymphocytic thymoma m	0	0	1	2	0	0	1	2	0	0	0	0	0	0	0	0
Carcinoma m	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
THYROID																
Follicular adenoma b	5	10	1	2	0	0	6	12	3	6	0	0	0	0	2	4
Follicular adenocarcinoma m	0	0	0	0	1	2	0	0	1	2	1	2	0	0	0	0
Parafollicular adenoma b	9	18	1	2	0	0	3	6	6	12	1	2	1	2	0	0
Parafollicular adenocarcinoma m	2	4	1	2	0	0	0	0	0	0	1	2	0	0	0	0
Hibernoma m	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
TONGUE																
Granular cell tumour b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
URINARY BLADDER																
Transitional cell papilloma b	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0

Appendix 1 (Continued) – Incidence and % Incidence of Neoplastic Lesions by Tissue for Terminal Kill and Interim Death Animals Combined (Page 65 of the Study Report)

	MALES								FEMALES							
	0ppm		1500ppm		5000ppm		15000ppm		0ppm		1500ppm		5000ppm		15000ppm	
Number of Rats	51		51		51		51		51		51		51		51	
CONDITION	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
UTERUS																
Endometrial stromal polyp b									7	14	5	10	4	8	8	16
Adenocarcinoma m									6	12	6	12	4	8	5	10
Stromal sarcoma m									1	2	0	0	0	0	1	2
Leiomyoma b									2	4	0	0	1	2	1	2
Angiosarcoma m									0	0	1	2	0	0	0	0
ABDOMINAL																
Adenocarcinoma m	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0
Anaplastic carcinoma m	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0
LYMPHOID/HAEMOPOIETIC																
Malignant lymphoma m	0	0	1	2	1	2	0	0	2	4	0	0	1	2	0	0
OVERALL TUMOUR INCIDENCE																
Primary benign tumours	27	53	17	33	17	33	29	57	28	55	22	43	20	39	32	63
Primary malignant tumours	14	28	10	20	11	22	5	10	15	29	11	22	10	20	12	24
Multiple benign tumours	17	33	9	18	4	8	17	33	28	55	13	26	14	28	21	41
Multiple malignant tumours	4	8	2	4	1	2	0	0	1	2	3	6	0	0	1	2

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:** Ray Kent
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: 24-Month Oral Chronic Toxicity and Carcinogenicity Study in Rats – Rat (83-5)

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 49987401

TEST MATERIAL (Purity): Glyphosate (96-96.8%)

SYNONYMS:

CITATION: Suresh, T.P. (1994) Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Toxicology Department Rallis Research Centre, Rallis India Limited, TOXI-1559, 002/1-GPT-CARCI-M. MRID 49987401. Unpublished.

SPONSOR: M/s Fiechemie Schwebda GmbH, Eupener Strabe 150, 50933, KOLN, Germany

EXECUTIVE SUMMARY:

In a combined chronic/carcinogenicity study (MRID 49987401), glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10000 ppm glyphosate for 24 months (0, 7.4, 73.9, and 740.6 mg/kg/day [M/F]). In addition, one vehicle control with 20 rats (10 males and 10 females) and one high dose treatment group with 40 rats (20 males and 20 females) were also included for interim sacrifice at the 12th month to study non-neoplastic histopathological changes. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

No adverse effects on survival were observed in either sex across the doses tested. There were no significant non-neoplastic lesions at any dose level in either sex and there were no statistically significant increases in any tumor type.

The agency performed a search of the pathology report to identify tumor types with potential monotonic dose responses in the various tissue types. No significant increases in tumor incidences were identified. In appendices 1 and 2, the total tumor incidences are listed for male and females respectively.

Based upon the results in this study, the NOAEL is ≥ 10,000 ppm (740.6 mg/kg/day). A LOAEL was not established.

There was no evidence of treatment-related neoplastic lesions in this study.

CLASSIFICATION

This carcinogenicity study in Wistar rats is **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study [OCSPP 870.4200; OECD 451] in rats.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. A Data Confidentiality statement was not located in the study report.

Appendix 1 - Total Tumor Incidences in Males (All animals)

Incidence	Group:	control	low*	mid*	high
		MALE			
No. of rats examined		50	50	50	50
No. of rats with neoplasm(s)		41	39	34	41
No. of benign neoplasms		53	34	26	49
No. of malignant neoplasms		27	35	28	32
No. of metastatic neoplasms		3	4	3	3

*: Terminally sacrificed animals showing gross lesions and masses have only been examined.

Data taken from page 83 of the study report.

Appendix 2 - Total Tumor Incidences in Females Combined sexes (All animals)

Incidence	Group: control	low*	mid*	high
FEMALE				
No. of rats examined	50	50	49	50
No. of rats with neoplasm(s)	27	36	36	28
No. of benign neoplasms	32	39	44 +	34
No. of malignant neoplasms	17	17	23	11
No. of metastatic neoplasms	3	1	2	0
COMBINED				
No. of rats examined	100	100	99	100
No. of rats with neoplasm(s)	68	75	70	69
No. of benign neoplasms	85	73	70	83
No. of malignant neoplasms	44	52	51	53
No. of metastatic neoplasms	6	5	4	3

*: Terminally sacrificed animals showing gross lesions and masses have only been examined.

Statistical analysis (inter group comparison by Z-test) of the above data has shown that:

a. The number of rats with neoplasms was similar in all the study groups for male, female and combined sex.

b. The incidence of benign tumours was low in the low and mid dose group males and combined sex, however in the mid dose group females it was high. None of these incidences showed dose correlation.

Data taken from page 84 of the study report.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent **Signature:**
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 44320620

TEST MATERIAL (Purity): Glyphosate Acid (99.2%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Davies, D.J., (1996) Glyphosate Acid: Excretion and Tissue Retention of a Single Oral dose (10 mg/kg) in the Rat. Zeneca Ag Products. Report No: CTL/4940, Study No: UR0506. MRID 44320620. Unpublished.

SPONSOR: Zeneca Ag Products

EXECUTIVE SUMMARY:

In a metabolism study (MRID 44320620), five male and five female Alpk: AP_fSD rats were each given single oral doses of 10 mg [^{14}C]-phosphonomethyl labelled glyphosate acid/kg. The excretion of radioactivity in urine and feces was monitored for 72 hours after dosing. After this period, the rats were killed and the residual activity was measured in blood, selected tissues and in the residual carcasses.

Excretion of radioactivity was rapid for rats of both sexes and most of the administered dose was eliminated, principally in the feces, within 24 hours. Males excreted means of 13.0% and 88.5% of the dose in urine and feces respectively for 72 hours. Females excreted means of 10.6% and 88.7% of the dose in urine and feces respectively over the same period. The rates of excretion or radioactivity in urine and feces were similar for male and female rats. The bone (femur) was the tissue with highest level of detectable compound at study termination (~0.4-0.5 µg equivalents glyphosate acid/g tissue).

CLASSIFICATION

These combined metabolism studies in Alpk: AP_fSD rats is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:** Ray Kent
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 44320621

TEST MATERIAL (Purity): Glyphosate Acid (99.2%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Davies, D.J., (1996) Glyphosate Acid: Excretion and Tissue Retention of a Single Intravenous dose (10 mg/kg) in the Rat. Zeneca Ag Products. Report No: CTL/4941, Study No: UR0508. MRID 44320621. Unpublished.

SPONSOR: Zeneca Ag Products.

EXECUTIVE SUMMARY:

In a metabolism study (MRID 44320621), five male and female Alpk: AP_fSD rats were given a single intravenous dose of 10 mg [^{14}C]-phosphonomethyl labelled glyphosate acid/kg. The excretion of radioactivity in urine and feces was monitored for 72 hours after dosing. After this period, the rats were killed and the residual activity was measured in blood, selected tissues and in the residual carcasses.

Excretion of radioactivity was rapid for rats of both sexes and most of the administered dose was eliminated, principally in the urine, within 24 hours. Males excreted means of 88.3% and 5.1% of the dose in urine and feces respectively for 72 hours. Females excreted means of 74.6% and 14.2% of the dose in urine and feces respectively over the same period. The rates of excretion or radioactivity in urine and feces were similar for male and female rats. Consistent with the single oral dose study, the bone (femur) was the tissue with highest level of detectable compound at study termination. Through I.V. administration, this value was roughly 10-fold greater than via the single oral dose administration (~3 vs 0.4-0.5 µg equivalents glyphosate acid/g tissue).

CLASSIFICATION

These combined metabolism studies in Alpk: AP$_f$SD rats is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anw Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:** Ray Kent
Senior Scientist, Health Effects Division (7509P) **Date:** 09/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 44320622

TEST MATERIAL (Purity): Glyphosate Acid (99.2%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Davies, D.J., (1996) Glyphosate Acid: Excretion and Tissue Retention of a Single Oral dose (1,000 mg/kg) in the Rat. Zeneca Ag Products. Report No: CTL/4942, Study No: UR0507. MRID 44320622. Unpublished.

SPONSOR: Zeneca Ag Products.

EXECUTIVE SUMMARY:

In a metabolism study (MRID 44320622), five male and five female Alpk: AP$_f$SD rats were each given single oral doses of 1,000 mg [^{14}C]-phosphonomethyl labelled glyphosate acid/kg. The excretion of radioactivity in urine and feces was monitored for 72 hours after dosing. After this period, the rats were killed and the residual activity was measured in blood, selected tissues and in the residual carcasses.

Excretion of radioactivity was rapid for rats of both sexes and most of the administered dose was eliminated, principally in the feces, within 24 hours. Males excreted means of 16.7% and 89.6% of the dose in urine and feces respectively for 72 hours. Females excreted means of 17.5% and 84.5% of the dose in urine and feces respectively over the same period. The rates of excretion or radioactivity in urine and feces were similar for male and female rats. Seventy-two hours after dosing, the mean total percentage of administered radioactivity present in all of the tissues examined and the residual carcass was 0.5% for males and 0.6% for females. The amounts present in the intestinal tract plus contents were 0.2% for both sexes.

CLASSIFICATION

These combined metabolism studies in Alpk: AP$_f$SD rats is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:** Anwar Y. Dunbar
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:** Ray Kent
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 44320623

TEST MATERIAL (Purity): Glyphosate Acid (99.2%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Davies, D.J., (1996) Glyphosate Acid: Excretion and Tissue Retention following Repeated Oral dosing (10 mg/kg) in the Rat. Zeneca Ag Products. Report No: CTL/4944, Study No: UR0517. MRID 44320623. Unpublished.

SPONSOR: Zeneca Ag Products.

EXECUTIVE SUMMARY:

In a metabolism study, five male and five female Alpk: AP$_f$SD rats were each given single oral doses of 10 mg [^{14}C]-phosphonomethyl labelled glyphosate acid/kg following the daily administration of unlabeled glyphosate acid (10 mg/kg) for the previous 14 days. The excretion of radioactivity in urine and feces was monitored for 72 hours after dosing. After this period, the rats were killed and the residual activity was measured in blood, selected tissues and in the residual carcasses.

Excretion of radioactivity was rapid for rats of both sexes and most of the administered dose was eliminated, principally in the feces, within 24 hours. Males excreted means of 10.6% and 88.6% of the dose in urine and feces respectively for 72 hours. Females excreted means of 10.7% and 90.7% of the dose in urine and feces respectively over the same period. The rates of excretion or radioactivity in urine and feces were similar for male and female rats. The amount of compound detected in the bone is similar to the values reported in the single oral dose study indicating that repeated low does not cause tissue accumulation.

CLASSIFICATION

These combined metabolism studies in Alpk: AP_fSD rats is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent, Ph.D. **Signature:**
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 44320624

TEST MATERIAL (Purity): Glyphosate Acid (99.2%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Macpherson, D. (1996) Glyphosate Acid: Biotransformation in the Rat. Zeneca Ag Products. Report No: CTL/5058, Study No: UR0511. MRID 44320624. Unpublished.

SPONSOR: Zeneca Ag Products.

EXECUTIVE SUMMARY:

In a metabolism study (MRID 44320624), the biotransformation of glyphosate acid was investigated in male and female rats previously given either 10 mg/kg or 1000 mg/kg oral dose of [^{14}C]-phosphonomethyl labelled glyphosate acid following repeated administration of the same dose of unlabeled compound. The role of biliary elimination was investigated following oral administration of [^{14}C]-glyphosate acid to bile duct cannulated rats. Excreted radioactivity was characterized by chromatographic and spectroscopic techniques.

Following an oral dose of [^{14}C]-glyphosate acid to bile duct cannulated rats the excretion of radioactivity in bile is negligible. The radioactivity present in urine and feces from rats given [^{14}C]-glyphosate acid at low or high dose levels, or after repeated dosing was characterized as being predominantly glyphosate acid. Trace amounts of aminomethyl phosphonic acid (AMPA) were detected in urine samples.

Following an oral dose of glyphosate acid to biliary-cannulated rats, approximately 21% of the dose was absorbed based upon the amount of radiolabel detected in the urine after 48 hours. The feces

and the bile accounted for 39.134%, respectively. The cage wash at 48 hours accounted for 2.534% of the radiolabel. The total excreted was 62.538%. For females, the amount excreted in the urine, feces and bile were 16.275%, 30.544% and 0.062% respectively. The cage wash account for 5.097% of the radiolabel and the total excreted was 51.978%. The unabsorbed glyphosate acid was excreted unchanged in feces. The absorbed dose was excreted in urine as glyphosate acid and trace amounts of AMPA.
While this study does generate findings which inform glyphosate's ADME profile, the Mass Balance was lower than in other studies; 62.538%-51.978% versus ≥ 90%.

CLASSIFICATION

These combined metabolism studies in Alpk: AP$_f$SD rats are classified **Acceptable/Guideline** and partially satisfy the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 09-07-16
EPA Secondary Reviewer: Ray Kent **Signature:**
Senior Scientist, Health Effects Division (7509P) **Date:** 9/7/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 44320625

TEST MATERIAL (Purity): Glyphosate Acid (99.2%)

SYNONYMS: Roundup®, N-(Phosphonomethyl) glycine

CITATION: Davies, D.J., (1996) Glyphosate Acid: Whole Body Autoradiography (10 mg/kg) in the Rat. Zeneca Ag Products. Report No: CTL/4942, Study No: UR0509. MRID 44320625. Unpublished.

SPONSOR: Zeneca Ag Products.

EXECUTIVE SUMMARY:

In a metabolism study (MRID 44320625), two male and female rats per dose were killed 24 and 48 hours after receiving a single oral dose of 10 mg [^{14}C]-phosphonomethyl labelled glyphosate acid/kg. The distribution of radioactivity was investigated using whole body autoradiography. In addition, the excretion of radioactivity was monitored in urine, feces and exhaled carbon dioxide.

Twenty-four hours after dosing, males excreted means of 22.3% and 55.5% of the administered dose in the urine and feces, respectively. Females excreted means of 11.9% and 83.8% of the administered dose, in the urine and feces, respectively, over the same period. Less than 0.2% of the administered dose was excreted as carbon dioxide over 24 hours after dosing. Forty-eight hours after dosing, the remaining male rat excreted 34.0% and 60.5% of the administered dose, in the urine and feces, respectively. The remaining female rat excreted 12.5% and 91.2% of the administered dose, in the urine and feces, respectively, over the same period.

The whole body autoradiograms showed no marked differences in the tissue distribution of radioactivity between male and female rats. All autoradiographs showed that a large proportion of

the radioactivity was present in the bone. Radiolabel was observed in the intestinal tract and contents of both sexes at 24 hours after dosing, with lesser amounts being present after 48 hours. Radiolabel was also apparent in the kidneys of both sexes 24 hours after dosing, reducing to negligible amounts after 48 hours.

CLASSIFICATION

These combined metabolism studies in Alpk: AP$_f$SD rats is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.

EPA Primary Reviewer: Anwar Y. Dunbar, Ph.D. **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:**
EPA Secondary Reviewer: Ray Kent **Signature:**
Senior Scientist, Health Effects Division (7509P) **Date:** 9/1/2016

ABBREVIATED DATA EVALUATION RECORD

TXR NO: 0057492

STUDY TYPE: Metabolism - Rat; OCSPP 870.7485 [§85-1]; OECD 417.

DP BARCODE: D435568

P.C.CODE.: 417300

MRID NO.: 47007906

TEST MATERIAL (Purity): N-Acetyl-glyphosate (99.2%)

SYNONYMS: None

CITATION: Cheng, T., Howard, S. (2004) Mass Balance, Metabolism, and Pharmacokinetics of [^{14}C]-N-Acetyl-glyphosate Following Administration of a Single Oral Dose to Rats. Pioneer Hi-Bred International Inc. Covance 7535-100, CMS 56245A. MRID 47007906. Unpublished.

SPONSOR: Zeneca Ag Products.

EXECUTIVE SUMMARY:

In a metabolism study (MRID MRID 47007906), the pharmacokinetics, absorption, elimination and metabolism were studied in male rats following a single oral administration of [^{14}C] N-acetyl-glyphosate at a nominal dose of 15 mg free acid equivalent/kg. Forty-five animals were tested. Blood was collected from four animals/time point pre-dose, and at 0.5, 1, 2, 4, 8, 12, 24, 48, and 72 hours post dose. Excreta were collected from 5 animals at specified intervals through 168 hours post dose. Plasma, excreta and carcass were analyzed for radioactivity content by using liquid scintillation counting (LSC). Selected samples of plasma, urine, and feces were analyzed for unchanged parent compound and metabolites.

The mean total recovery of radioactivity was 95.5%, with 66.1% in urine, 26.4% in feces, 2.79% in cage wash and wipe, and 0.23% in the residual carcass. These values do not include data for animal no. C16498, which had suspected urine contamination of the feces. More than 90% of the radioactivity was eliminated by 48 hours post dose.

The mean maximum concentrations (Cmax) in blood and plasma were 2.93 and 5.31 μg equivalents/g at 1 and 2 hours post dose, respectively. Radioactivity was eliminated from blood and plasma with half-life (t1/2) values of 20.1 and 15.6 hours, respectively. Comparison of blood and plasma values for area under the curve (AUC) indicates that [^{14}C] N-acetyl-glyphosate distributed preferentially into plasma.

Unchanged [^{14}C] N-acetyl-glyphosate recovered in urine and feces represented over 99% of the administered radioactivity. A metabolite, glyphosate, was detected in feces and represented less than 1% of the total radioactivity. Plasma radioactivity consisted entirely of unchanged [^{14}C] N-acetyl-glyphosate.

CLASSIFICATION

The combined metabolism studies in Alpk: AP$_f$SD rats is classified **Acceptable/Guideline** and satisfies the guideline requirement for a metabolism study [OCSPP 870.7485, OECD 417] in rats.